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September 19, 2007.

David Saliwanchik

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RESPONSE UNDER 37 CFR 1.116
Examining Group 1649
Patent Application
Docket No. BB-138

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	John D. Ulm
Art Unit	:	1649
Applicants	:	Bernd Bufe *et al.*
Serial No.	:	10/528,630
Conf. No.	:	7026
Filed	:	June 29, 2005
For	:	Bitter Taste Receptors

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Commissioner for Patents
P.O. Box 1450
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AMENDMENT UNDER 37 CFR 1.116

Sir:

In response to the Office Action dated June 27, 2007, please amend the above-referenced application as follows:

Amendments to the claims begin on page 2 of this paper.

Remarks/Arguments follow the amendment section.

In the Claims

This listing of claims will replace all prior versions and listings of claims in this application.

1 - 14 (Cancelled).

15 (Currently amended). A process for ~~isolating~~identifying an antagonist of the bitter taste receptor activity of the polypeptide encoded by a polynucleotide selected from the group consisting of:

(a) a polynucleotide encoding at least a mature form of a polypeptide having [[a]]the deduced amino acid sequence as shown in SEQ ID NO: 1;

(b) a polynucleotide having [[a]]the coding sequence, as shown in SEQ ID NO: 2 encoding at least a mature form of the polypeptide having the deduced amino acid sequence as shown in SEQ ID NO:1;

(c) a polynucleotide encoding a ~~fragment or~~ derivative of a polypeptide encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one to twenty ~~or more~~ amino acid residues are conservatively substituted compared to said polypeptide, and said ~~fragment or~~ derivative has bitter taste receptor activity when contacted with an agonist selected from the group consisting of acetylthiourea, N,N-dimethylthioformamide, N,N'-diphenylthiourea, N-ethylthiourea, 2-imidazolidinethione, 4)6)-methyl-2-thiouracil, N-methylthiourea, phenylthiocarbamide, 6-phenyl-2-thiouracil, 6-propyl-2-thiouracil, tetramethylthiourea, thioacetamide, thioacetanilide, 2-thiobarbituric acid and 2-thiouracil;

(d) a polynucleotide which is at least ~~50%~~ 85% identical to a polynucleotide as defined in any one of (a) to (c) and which ~~codes for~~ encodes a polypeptide having bitter taste receptor activity when contacted with an agonist selected from the group consisting of acetylthiourea, N,N-dimethylthioformamide, N,N'-diphenylthiourea, N-ethylthiourea, 2-imidazolidinethione, 4(6)-methyl-2-thiouracil, N-methylthiourea, phenylthiocarbamide, 6-phenyl-2-thiouracil, 6-propyl-2-thiouracil, tetramethylthiourea, thioacetamide, thioacetanilide, 2-thiobarbituric acid and 2-thiouracil; and

(e) a polynucleotide the complementary strand of which hybridizes under ~~moderate~~ high

stringency hybridization conditions to a polynucleotide as defined in any one of (a) to (d) and which ~~codes for~~ encodes a polypeptide having bitter taste receptor activity when contacted with an agonist selected from the group consisting of acetylthiourea, N,N-dimethylthioformamide, N,N'-diphenylthiourea, N-ethylthiourea, 2-imidazolidinethione, 4(6)-methyl-2-thiouracil, N-methylthiourea, phenylthiocarbamide, 6-phenyl-2-thiouracil, 6-propyl-2-thiouracil, tetramethylthiourea, thioacetamide, thioacetanilide, 2-thiobarbituric acid and 2-thiouracil;

wherein said process comprises the steps of:

(1) contacting said polypeptide, or a host cell genetically engineered with said polynucleotide or with a vector containing said polynucleotide, with an agonist of bitter taste receptor activity selected from the group consisting of acetylthiourea, N,N-dimethylthioformamide, N,N'-diphenylthiourea, N-ethylthiourea, 2-imidazolidinethione, 4(6)-methyl-2-thiouracil, N-methylthiourea, phenylthiocarbamide, 6-phenyl-2-thiouracil, 6-propyl-2-thiouracil, tetramethylthiourea, thioacetamide, thioacetanilide, 2-thiobaarbituric acid, 2-thiouracil and functional derivatives thereof;

(~~1~~2) contacting said polypeptide, or a host cell genetically engineered with said polynucleotide or with a vector containing said polynucleotide, with a potential antagonist; and

(~~2~~3) determining whether the potential antagonist antagonizes the bitter taste receptor activity of said polypeptide.

16 (currently amended). The process of claim 15 ~~further comprising the contacting of the polypeptide with an agonist of the respective bitter taste receptor activity~~wherein steps (1) and (2) are carried out concomitantly.

17 (currently amended). The process of claim ~~16 in which said contacting with an agonist~~15 wherein step (2) is carried out prior to step (1)~~, concomitantly or after step (1) of claim 15~~.

18 (Cancelled).

19 (Currently amended). A process selected from the group consisting of:

A. a process for the production of a food or any precursor material or additive employed in the production of foodstuffs comprising the steps of: ~~either~~

~~(i) isolating a compound that binds to an isolated polypeptide encoded by an isolated polynucleotide selected from the group consisting of:~~

~~(a) a polynucleotide encoding at least a mature form of a polypeptide having a deduced amino acid sequence as shown in SEQ ID NO: 1;~~

~~(b) a polynucleotide having a coding sequence, as shown in SEQ ID NO: 2 encoding at least a mature form of the polypeptide;~~

~~(c) a polynucleotide encoding a fragment or derivative of a polypeptide encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said polypeptide, and said fragment or derivative has bitter substance binding activity;~~

~~(d) a polynucleotide which is at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which codes for a polypeptide having bitter substance binding activity; and~~

~~(e) a polynucleotide the complementary strand of which hybridizes under moderate hybridization conditions to a polynucleotide as defined in any one of (a) to (d) and which codes for a polypeptide having bitter substance binding activity;~~

~~wherein said isolating step further comprises:~~

~~(1) contacting said isolated polypeptide, or a host cell genetically engineered with said isolated polynucleotide or with a vector containing said isolated polynucleotide, with a compound;~~

~~(2) detecting the presence of the compound which binds to said polypeptide; and~~

~~(3) determining whether the compound binds said polypeptide;~~

~~or~~

~~(ii) isolating an antagonist of the bitter taste receptor activity of an isolated polypeptide encoded by an isolated polynucleotide selected from the group consisting of:~~

~~(a) a polynucleotide encoding at least a mature form of a polypeptide having a deduced amino acid sequence as shown in SEQ ID NO: 1;~~

~~(b) a polynucleotide having a coding sequence, as shown in SEQ ID NO: 2 encoding at least a mature form of the polypeptide;~~

~~(c) a polynucleotide encoding a fragment or derivative of a polypeptide encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said polypeptide, and said fragment or derivative has bitter taste receptor activity;~~

~~(d) a polynucleotide which is at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which codes for a polypeptide having bitter taste receptor activity; and~~

~~(e) a polynucleotide the complementary strand of which hybridizes under moderate hybridization conditions to a polynucleotide as defined in any one of (a) to (d) and which codes for a polypeptide having bitter taste receptor activity;~~

~~wherein said isolating step further comprises:~~

~~(1) contacting said isolated polypeptide, or a host cell genetically engineered with said isolated polynucleotide or with a vector containing said~~ isolated polynucleotide~~, with a potential antagonist; and~~

~~(2) determining whether the potential antagonist antagonizes the bitter taste receptor activity of said polypeptide;~~

~~and wherein the process further comprises the subsequent step of~~

(1) identifying an antagonist according to the process of claim 15; and

(2) admixing the identified ~~compound or~~ antagonist with a foodstuff ~~foodstuffs or any~~ precursor material or additive employed in the production of foodstuffs; and

B. a process for the production of a nutraceutical or pharmaceutical composition comprising the steps of; ~~either~~

~~(i) isolating a compound that binds to an isolated polypeptide encoded by an isolated polynucleotide selected from the group consisting of:~~

~~(a) a polynucleotide encoding at least a mature form of a polypeptide having a deduced amino~~

~~acid sequence as shown in SEQ ID NO: 1;~~

~~(b) a polynucleotide having a coding sequence, as shown in SEQ ID NO: 2 encoding at least a mature form of the polypeptide;~~

~~(c) a polynucleotide encoding a fragment or derivative of a polypeptide encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said polypeptide, and said fragment or derivative has bitter substance binding activity;~~

~~(d) a polynucleotide which is at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which codes for a polypeptide having bitter substance binding activity; and~~

~~(e) a polynucleotide the complementary strand of which hybridizes under moderate hybridization conditions to a polynucleotide as defined in any one of (a) to (d) and which codes for a polypeptide having bitter substance binding activity;~~

~~wherein said isolating step further comprises:~~

~~(1) contacting said isolated polypeptide, or a host cell genetically engineered with said isolated polynucleotide or with a vector containing said isolated polynucleotide, with a compound;~~

~~(2) detecting the presence of the compound which binds to said polypeptide; and~~

~~(3) determining whether the compound binds said polypeptide;~~

~~or~~

~~(ii) isolating an antagonist of the bitter taste receptor activity of an isolated polypeptide encoded by an isolated polynucleotide selected from the group consisting of:~~

~~(a) a polynucleotide encoding at least a mature form of a polypeptide having a deduced amino acid sequence as shown in SEQ ID NO: 1;~~

~~(b) a polynucleotide having a coding sequence, as shown in SEQ ID NO: 2 encoding at least a mature form of the polypeptide;~~

~~(c) a polynucleotide encoding a fragment or derivative of a polypeptide encoded by a polynucleotide of any one of (a) to (b), wherein in said derivative one or more amino acid residues are conservatively substituted compared to said polypeptide, and said fragment or derivative has bitter taste receptor activity;~~

~~(d) a polynucleotide which is at least 50% identical to a polynucleotide as defined in any one of (a) to (c) and which codes for a polypeptide having bitter taste receptor activity; and~~

~~(e) a polynucleotide the complementary strand of which hybridizes under moderate hybridization conditions to a polynucleotide as defined in any one of (a) to (d) and which codes for a polypeptide having bitter taste receptor activity;~~

~~wherein said isolating step further comprises:~~

~~(1) contacting said isolated polypeptide, or a host cell genetically engineered with said isolated polynucleotide or with a vector containing said isolated polynucleotide, with a potential antagonist; and~~

~~(2) determining whether the potential antagonist antagonizes the bitter taste receptor activity of said polypeptide;~~

~~and wherein the process further comprises the subsequent step of~~

(1) identifying an antagonist according to the process of claim 15; and

(2) formulating the identified ~~compound or~~ antagonist with an active agent in a pharmaceutically acceptable form.

20- 24 (Cancelled).

Remarks

Claims 1-5, 7, 9, 12 and 14-19 were pending in the subject application. By this Amendment, the applicants have amended claims 15-17 and 19 and have cancelled claims 1-5, 7, 9, 12 and 18. No new matter has been added by these amendments. Accordingly, claims 15-17 and 19 are now before the Examiner for consideration.

The amendments to the claims and specification have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution. Support for the claim amendments can be found throughout the specification and the claims as originally filed. The amendments should not be taken to indicate the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

The abstract of the disclosure has been objected to under 37 CFR 1.52(b)(4). Attached herewith is a new page 51, Abstract of the Disclosure.

Claims 1-5, 7, 9, 12, and 14-19 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The applicants respectfully traverse this ground for rejection to the extent that it might be applied to the claims now presented for examination.

By this Amendment, the applicants have cancelled claims 1-5, 7, 9, 12 and 14, thus rendering moot the rejection of these claims. Also, the applicants have amended claim 15 in order to lend greater clarity to the claimed subject matter.

Claim 15 is directed to a process for identifying an antagonist of the bitter taste receptor activity of a particular bitter taste receptor, namely hTAS2R38. The Office Action appears to acknowledge that polynucleotides according to alternatives (a) and (b) of claim 15 (polynucleotides encoding a polypeptide having the amino acid sequence as set out in SEQ ID NO:1) would be enabled for the claimed process of identifying an antagonist of bitter taste receptor activity. However, the Office Action indicates that alternatives (c) through (e) of the original (before the amendments set forth herein) claim 15 would not be enabled. These alternatives are directed at assays using polypeptides that are very closely related to, but not identical to, the specific polypeptide of alternatives (a) and (b).

As discussed more fully below, the applicants respectfully submit that a person skilled in the art could readily, and without undue experimentation, practice the full scope of the method now set forth in amended claim 15.

The hTAS2R38 taste receptor belongs to the seven transmembrane receptor superfamily that is also known as G protein-coupled receptors (GPCRs) (see page 1, lines 29-33 of the present application). The family of G protein-coupled receptors is one of the best studied receptor families as is evident from WO 01/077676, which teaches, for example, on page 2, line 26 through page 3, line 31, that the structure of G protein coupled receptors is well known. What remains unknown are the molecules and pathways that mediate a sensory receiving response (see page 3, lines 22-24 of WO 01/077676). This is further evidenced by the attached paper of T.H. Ji *et al.*, J.B.C. (1998) 273:17299-17302, which teaches on page 17299 left column that "[a]s shown in Fig. 1A, all GPCRs have an extracellular N-terminal segment, seven TMs [transmembrane domains], which form the TM core, three exoloops, three cytoloops and a C-terminal segment."

From the remainder of this text, in particular Fig. 1, it is clear that all G protein-coupled receptors and, in particular, the members of the taste receptor family, share high structural similarity. Accordingly, given this detailed state of knowledge in the art with respect to the structure of human taste receptors, a person of ordinary skill in the art can readily select regions for introducing mutations into the hTAS2R38 sequence and test those with the bitter tastants as set forth in the applicants' claims as amended herein. Given that the present application provides the bitter tastants that stimulate hTAS2R38, there is no undue burden to the skilled person, in view of the guidance provided in the specification and known from the prior art, to test a given variant of hTAS2R38 according to claim 15, as amended herein.

For an invention to be enabled under the first paragraph of §112, the specification need only teach a person of ordinary skill in the art "how to make" and "how to use" the invention. It is further noted that the sheer number of compounds which may fall within the scope of a claim is not determinative of the enablement of the specification. See, e.g., *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976), where the court observed that a large but finite list of materials, in combination with a teaching of how to carry out the invention, was enabling for purposes of §112.

It should be noted that the requirement for some experimentation and/or screening does not necessarily make a claim non-enabled. "Enablement is not precluded by the necessity for some experimentation such as routine screening. . . A considerable amount of experimentation is permissible, if it is merely routine . . ." (emphasis added). *In re Wands,* 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988). In the current case, any experimentation needed to identify other polypeptides would be routine given the guidance provided in the subject application. This guidance includes the extensive knowledge in the art concerning these polypeptides, the exemplification of specific polypeptides, as well as the provision of methods of assaying for activity.

The applicants are cognizant of the duty under §112, first paragraph, to provide sufficient teaching in the specification to enable one skilled in the art to practice the invention as claimed without undue experimentation. For the reasons set forth above, the applicants believe that they have fulfilled the requirements of 35 USC §112. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-5, 7, 9, 12 and 14-19 have been rejected under 35 U.S.C. §112, second paragraph. Claims 1, 3, 5, 7, 9, 12 and 14 have been cancelled, thus rendering moot this rejection as it applies to those claims.

Claim 15, alternative (a) has been amended to clarify that the polynucleotide encodes at least the mature form of the polypeptide having the deduced amino acid sequence as shown in SEQ ID NO:1. The applicants appreciate the Examiner's helpful input with regard to this claim languge.

Furthermore, alternative (b) of claim 15 has been amended herein to refer to "a polynucleotide having the coding sequence as shown in SEQ ID NO:2 encoding at least a mature form of the polypeptide having the deduced amino acid sequence as is shown in SEQ ID NO:1" (emphasis added). The applicants appreciate the Examiner's careful review of the claims and they believe that the amendments set forth herein address the issues identified by the Examiner. Further the applicants have amended claim 19 to incorporate the limitations of amended claim 15.

In view of the amendments to the claims, the applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Claims 1-5, 7, 9 and 14-19 have been rejected under 35 U.S.C. §102(a) as being anticipated by Adler (WO 01/77676). Also, claims 1-5, 7, 9 and 14-19 have been rejected under 35 U.S.C. §102(e) as being anticipated by Adler (U.S. Patent Publication US 20020094551). Claims 1-5, 7, 9 and 14 have been cancelled herein thus rendering moot this ground for rejection as it relates to those claims. Also, as noted above, claim 15 has been amended herein to lend greater clarity to the claimed subject matter. To the extent that this rejection may be applied to the claims now presented for examination, the applicants respectfully traverse this ground for rejection because the cited Adler references do not disclose or suggest the advantageous method claimed by the current applicants.

It is basic premise of patent law that, in order to anticipate, a single prior art reference must disclose within its four corners, each and every element of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra; Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

Neither of these prior documents provide any teaching with respect to bitter tastants that can be used to stimulate the activity of hTAS2R38, let alone the specific bitter tastants that are recited in the claims as amended herein. Thus, the claimed subject matter is neither anticipated by, nor obvious in view of, the two prior art documents. In that respect, please note that WO 01/077676 admits that much is known about the bitter taste receptors itself, but that nothing is known about the bitter tastants (see page 3, lines 22-24 of WO 01/077676).

In *Dewey v. Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention,

> it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

The provision of a bitter tastant capable of stimulating a particular bitter taste receptor, i.e. the so called "deorphanization" of a receptor, is of paramount importance to the identification of antagonists of this receptor. The activity of an unstimulated taste receptor cannot be further suppressed by any antagonists. Accordingly, the disclosures in the prior art documents are not enabling since no agonists are provided.

The applicants unique and advantageous method as set forth in the amended claims now presented for examination are not disclosed, or even suggested by, the cited references.

Therefore, the applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) based on the Adler references.

In view of the foregoing remarks, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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DRS/la

Attachment: Abstract

Abstract

The present invention relates to bitter-taste receptors and their role in bitter taste transduction. The invention also relates to assays for screening molecules that modulate, e.g. suppress or block bitter taste transduction, or enhance bitter taste response.